

REMARKS

Claims 46, 48-53, 58, 63, 65, and 66 have been amended by way of this amendment. Claims 31, 33-42, 44, 45, 47, 54-57, 61-62 have been cancelled, without prejudice or disclaimer, by way of this amendment. Claims 67-75 have been added by way of this amendment. The Examiner has indicated that claim 43 appears to be in condition for allowance. Claims 43, 46, 48-53, 58-60, 63-75 (of which 49-53 and 60 are currently withdrawn) remain pending in this application.

Claims 46, 48-53, and 63 have been amended to correct grammatical informalities (e.g. to recite "a method" rather than "the method"). In addition, claim 50 was amended to correct the spelling of the term "pyrimidine." Claims 46, 48, 49, and 58 have been amended to change the claim from which they depend and to make proper reference to the subject matter of the claim from which they now depend. No new matter has been added by way of these amendments.

Claim 63 has been amended to recite specific *udp* and *deoD* nucleotide sequences. This is supported by page 5, lines 8-11 of the specification and, for example, the descriptions in the sequence listing filed on June 25, 2001 of SEQ ID NO: 6, where it is stated that nucleotides 243 to 1021 correspond to the *udp* gene and that nucleotides 1037 to 1766 correspond to the *deoD* gene. Claims 65 and 66 have been amended to make proper reference to the subject matter of the claim from which they depend (claim 63; which is directed to a host cell). Accordingly, these claims have been amended to be directed to "a host cell" rather than "a plasmid vector." No new matter has been added by way of these amendments.

Support for new claim 67 can be found in originally filed claim 4 of PCT/EP99/10416 (the PCT application of which the instant application is a continuation application; herein "the '416 PCT application") and throughout the specification and, in particular, on page 5, lines 21-24; and page 7,

line 8 - page 9, line 18. Support for new claim 68 can be found in originally filed claim 10 of the '416 PCT application and throughout the specification and, in particular, on page 7, lines 4-5. Support for new claim 69 can be found in originally filed claim 11 of the '416 PCT application and throughout the specification and, in particular, on page 7, line 5. Support for new claim 70 can be found in originally filed claim 28 of the '416 PCT application and throughout the specification and, in particular, on page 6, lines 11-15.

New claims 71-75 depend from withdrawn claims 49, 51, and 52; the withdrawn claims from which they depend have been amended by way of the instant amendment to put their language into proper claim form. New claims 71-75 have been added to provide claims that are directed to the subject matter of claims 49, 51, and 52 that has been deleted from these claims by way of this amendment. The withdrawn claims are being amended to be put into proper form because the Examiner has acknowledged that if a product claim is found allowable, withdrawn process depending from or otherwise including all of the limitations of the allowable product claim will be rejoined in accordance with MPEP § 821.04. No new matter has been added by way of these new claims and Applicants respectfully request their consideration.

Support for new claim 71 can be found in originally filed claim 23 of the '416 PCT application and throughout the specification and, in particular, on page 13, line 28 - page 14, line 6. Support for new claim 72 can be found in originally filed claim 22 of the '416 PCT application and throughout the specification and, in particular, on page 13, line 29 - page 14, line 1. Support for new claim 73 can be found in originally filed claim 22 of the '416 PCT application and throughout the specification and, in particular, on page 14, line 1-6. Support for new claim 74 can be found in originally filed claim 24 of the '416 PCT application and throughout the specification and, in

components present in the environment in which they naturally occur, i.e., a cell. In fact, Krenitsky teaches that the cellular components may interfere with enzyme activity (“crude preparations catalyse undesirable alterations of substrates and products, and may even cause proteolysis of the required enzymes themselves”). Thus, Krenitsky teaches that in order to get high enzyme activity, the enzymes must be purified from their cellular environment. This is in direct contrast to the presently pending claims that are directed to “[a] transformed prokaryotic host cell expressing 120-1000 times higher uridine phosphorylase activity, purine nucleoside phosphorylase activity or both, than the corresponding non-transformed prokaryotic host cell.” Thus, the enzyme, as expressed, has higher activity before and without any need for purification.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990); (MPEP 2143.01). In the instant case, when considering Krenitsky as a whole, it cannot be combined with the other references, as suggested by the Examiner, to arrive at transformed host cell expressing 120-1000 times higher uridine phosphorylase activity, because it teaches away from the present invention.

Implicit in Krenitsky is an admission that as expressed, the enzyme activities do not have high activity. If they did, Krenitsky would not be so concerned with loss of such activity as to provide the forgoing forceful negative teaching.

• The Claimed Invention Requires “As Expressed” Enzyme Activities Not Taught by the Art

As discussed above, because of its teachings as a whole, Krenitsky cannot be combined with the other references. For this reason alone, the claims are unobvious over the combinations of references suggested by the Examiner. However, even when forcefully combining Krenitsky with the references proposed by the Examiner, the resulting combination does not achieve the results seen by the inventors with the presently claimed cells.

In the Action the Examiner states (page 15, second-to last line - page 16, line 7):

[o]ne would have a reasonable expectation of success that, by using the pET29c vector [taught in Novagen 1997] for expression of genes encoding E. coli UDP and PNP, a high yield of expression would be obtained. In this regard, the Office does not have the facilities for examining and comparing applicants' UDP and/or PNP activity in the host cells of claims 61-66 with that of the prior art. Thus, the burden is on the applicant to show a novel or nonobvious difference between the claimed product and the product of the prior art (i.e. that the level of UDP and PNP activity as expressed in an E. coli host using the pET29C vector does not possess the same material characteristics of the claimed host cell.) See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.* 205 USPQ 594.

As discussed in detail below, the presently claimed invention is directed to host cells expressing UdP and PNP activity levels that were surprising over those reported in the art. The high level of enzyme activity achieved in these cells is demonstrated in the specification in the following passage (page 12, first full paragraph):

The surprisingly high level of enzyme activity of these novel recombinant strains is confirmed by an indirect comparison with the strains described in JP-06-253854: the strains considered in the present invention permit enzyme activities from 340 to 1040 times (as regards the activity of UdP) and from 120 to 200 times (as regards the

Accordingly, since Krenitsky teaches that thermophilic and mesophilic enzymes are both effective, and since Noguchi essentially shows that thermophilic enzymes are not particularly effective, it is surprising that the presently claimed cells achieve up to 1040 and 200 times UdP and PNP activity, respectively, even at 30 °C (specification at page 12, 1st paragraph).

The high level of enzyme activity achieved in the claimed cells is also demonstrated in the specification in the following passage (page 10, lines 8-17 and last paragraph):

The efficiency of these novel strains, both as producers of the enzymes PNP and UdP and as biocatalysts for the preparation of nucleosides by bioconversion reactions, was compared with a preparation of *Enterobacter aerogenes* cells cultivated in the presence of inducers because that micro-organism, according to the data available in the literature, has hitherto been regarded as one of the best for catalysing transglycosylation reactions (Utagawa et al., *Agric.Biol.Chem.* 49, 1053-1058, 1985; Utagawa et al., *Agric.Biol.Chem.* 49, 2711-2717, 1985).

Applying that test, the enzyme activities of UdP and PNP were measured in the recombinant bacterial strains to which the present invention relates and in the comparison *E. aerogenes* strain, ... which show that the recombinant strains of the present invention have enzyme activities up to approximately 10-30 times higher than that of the comparison strain cultivated under induction conditions and up to approximately 120-1000 times higher than that of the non-transformed *E. coli* host strains.

These results demonstrate that even if Krenitsky didn't teach away from the present invention and if, for the sake of argument, one had been motivated to combine Krenitsky with Walton, Hershfield, Bulow and Novagen or to combine Krenitsky with Walton, Hershfield, Bulow and Sambrook, one could not have expected or predicted the high activity levels seen in the presently claimed cells. Specifically, higher levels of UdP and PNP activity was seen from the

claimed host cells, which were not induced, than in induced cells which at the time of the present invention were considered the best for catalyzing such reactions.

For all of the above reasons, it is respectfully submitted that the pending claims are unobvious over any combination of the references cited by the Examiner.

Lastly, the Examiner has rejected claim 33 as being allegedly obvious over Krenitsky in view of Walton, Hershfield, Bulow, and Sambrook and further in view of Noguchi (JP 6-253854).

As claim 33 has been cancelled by way of this amendment, this rejection is moot and Applicants respectfully request its withdrawal.

Rejoinder of Withdrawn Process Claims

The Examiner has withdrawn the currently pending process claims of group II (claims 49-53) from Examination under 37 C.F.R. 1.142(b), but has acknowledged that if a product claim is found allowable, withdrawn process claims depending from or otherwise including all of the limitations of the allowable product claim will be rejoined in accordance with MPEP § 821.04 (see page 2 of Action mailed December 11, 2003). Accordingly, these withdrawn process claims have been amended to correct any informalities and to keep the language of the claims consistent with the currently pending product claims. Rejoinder of any currently withdrawn process claim that depends from or otherwise includes all of the limitations of any allowable product claim in the instant application is earnestly solicited.

CONCLUSION

In view of the accompanying amendments and remarks, reconsideration of this application and allowance of all pending claims and rejoinder of the process claims is respectfully requested. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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